BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

some page have Lines

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

IPW

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of:		Atty. Docket No.:	6794A-000061/US/COG 3272/03/US
BARTON et al.			
Serial No.:	**10/727,681**	Group Art Unit:	TBA
Filed:	December 4, 2003	Examiner:	TBA

For: Eplerenone Crystal Form Exhibiting Enhanced Dissolution Rate

PETITION RE NOTICE OF INCOMPLETE NONPROVISIONAL APPLICATION

Office of Petitions
Mail Stop Petitions
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

A Notice of Incomplete Nonprovisional Application (hereinafter "Notice") was mailed on May 18, 2004 in connection with the above-identified application. The Notice states the following requirements have yet to be met:

(1) A newly executed Oath or Declaration is required;

(2) A set of drawings has to be provided because this Notice asserts that "the application was deposited without drawings;" and

(3) Replacement pages 1-6, 10, 21-28, 35, 41, 48-49, 52, 54, 59-60, 62, 64-66, and 69 are requested.

The first requirement is not necessary because the second requirement has been fulfilled for the reasons noted below. In particular, the above-identified application is "a continuation under 37 CFR §1.53(b) of pending prior parent application of serial no. 09/732,208, filed on December 7, 2000." Attached to this Petition is a copy of the transmittal papers associated with the filing of the subject continuation application filed under 37 CFR §1.53(b). On page 2 of that transmittal paper, there is a "X" marked before the sentence "Transfer the drawings from the prior

application to this application and abandon said prior application as of the filing date accorded this application." In view of the foregoing, there was no need to file a separate set of drawings in this subject continuation application because those drawings were previously filed with the parent application of serial no. 09/732,208 which were supposed to be transferred into the file of this application.

Also, with respect to the second requirement, the Notice requires a new Oath or Declaration. Again, there is no need for a new Oath or Declaration because no new drawings are being submitted. Further, an Oath was already filed. In fact, on page 1 of the transmittal of the filing of the subject continuation application under 37 CFR §1.53(b) there is a "X" marked before the sentence "Enclosed is a copy of the prior application, including the oath or declaration as original filed December 7, 2000. I hereby verify that the papers are a true copy of said prior application as originally filed on December 7, 2000."

With respect to the third requirement upon telephonic inquiry regarding same of Ms. Robinson at the USPTO on July 13, 2004, she indicated that these pages contained extraneous underlining and other markings necessitating clean replacement pages.

In view of the foregoing submission of transmittal papers, there is no need for either (1) the re-submission of a set of drawings or (2) the submission of a newly-executed Oath or Declaration.

However, to satisfy the third requirement we enclose replacement pages 1-6, 10, 21-28, 35, 41, 48-49, 52, 54, 59-60, 62, 64-66, and 69.

Please find attached a check in the amount of $130 for the requisite petition fee. However, since the requirement to file this petition is due to U.S. Patent and Trademark Office (USPTO) error, Applicants request a refund of this petition fee. Such refund should be credited to our Deposit Account No. 08-0750.

No additional fees are believed to be due. However, should any additional fees be required or an overpayment of fees made, please debit or credit our Deposit Account No. 08-0750, as necessary.

Prompt consideration of this Petition is earnestly solicited. Additionally, a copy of an executed Associate Power of Attorney and Change of Address in favor of the attorneys at Harness, Dickey & Pierce, P.L.C. is attached hereto.

Respectfully submitted,

Date: July 16, 2004

Ajay Pathak
Registration No. 38, 266

Enclosures:

- Associate Power of Attorney and Change of Address
- Copy of transmittal papers previously filed with this application when filed under 37 CFR §1.53(b)
- Duplicate Drawing Set
- Duplicate Declaration
- Copy of Notice of Incomplete Non-Provisional Application
- Fee Transmittal Sheet
- Replacement Pages 1-6, 10, 21-28, 35, 41, 48-49, 52, 54, 59-60, 62, 64-66, and 69 from specification (without extraneous markings)

HARNESS, DICKEY & PIERCE, P.L.C.
11780 Plaza America Drive, Suite 600
Reston, Virginia 20190
(703) 668-8000 (general office line)
(703) 668-8033 (direct line for Mr. Pathak)
(703) 668-8200 (office fax line)

PTO/SB/17 (10-01)
Approved for use through 10/31/2002. OMB 0651-0032
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

FEE TRANSMITTAL for FY 2004

Patent fees are subject to annual revision.

	Complete if Known
Application Number	10/727,681
Filing Date	December 4, 2003
Inventor(s)	BARTON et al.
Examiner Name	TBA
Group Art Unit	TBA
Attorney Docket No.	6794A-000061/US/COG

TOTAL AMOUNT OF PAYMENT ($) 130.00

METHOD OF PAYMENT (check one)

1. ☒ The Commissioner is hereby authorized to charge indicated fees and credit any over payments to:

Deposit Account Number: 08-0750

Deposit Account Name: Harness, Dickey & Pierce, P.L.C.

☒ Charge Any Additional Fee Required Under 37 CFR 1.16 and 1.17

☐ Applicant claims small entity status. See 37 CFR 1.27

2. ☒ Payment Enclosed:

☒ Check ☐ Credit card ☐ Money Order ☐ Other

FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1001	770	2001	385	Utility filing fee	
1002	340	2002	170	Design filing fee	
1003	530	2003	265	Plant filing fee	
1004	770	2004	385	Reissue filing fee	
1005	160	2005	80	Provisional filling fee	

SUBTOTAL (1) ($) 0

2. EXTRA CLAIM FEES

			Extra Claims		Fee from below	=	Fee Paid
Total Claims		-20 **		X		=	
Independent Claims		-3 **		X		=	
Multiple Dependent				X		=	

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
1202	18	2202	9	Claims in excess of 20
1201	86	2201	43	Independent claims in excess of 3
1203	290	2203	145	Multiple dependent claim, if not paid
1204	86	2204	43	** Reissue independent claims over original patent
1205	18	2205	9	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($)

**or number previously paid, if greater; For Reissues, see above

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1051	130	2051	65	Surcharge - late filing fee or oath	
1052	50	2052	25	Surcharge - late provisional filing fee or cover sheet.	
1053	1053	1053	130	Non-English specification	
1812	2,520	1812	2,520	For filing a request for reexamination	
1804	920*	1804	920*	Requesting publication of SIR prior to Examiner action	
1805	1,840*	1805	1,840*	Requesting publication of SIR after Examiner action	
1251	110	2251	55	Extension for reply within first month	
1252	420	2252	210	Extension for reply within second month	
1253	950	2253	475	Extension for reply within third month	
1254	1,480	2254	740	Extension for reply within fourth month	
1255	2,010	2255	1,005	Extension for reply within fifth month	
1401	330	2401	165	Notice of Appeal	
1402	330	2402	165	Filing a brief in support of an appeal	
1403	290	2403	145	Request for oral hearing	
1451	1,510	1451	1,510	Petition to institute a public use proceeding	
1452	110	2452	55	Petition to revive – unavoidable	
1453	1,330	2453	665	Petition to revive – unintentional	
1501	1,330	2501	665	Utility issue fee (or reissue)	
1502	480	2502	240	Design issue fee	
1503	640	2503	320	Plant issue fee	
1460	130	1460	130	Petitions to the Commissioner	130
1807	50	1807	50	Processing fee under 37 CFR 1.17 (q)	
1806	180	1806	180	Submission of Information Disclosure Stmt	
8021	40	8021	40	Recording each patent assignment per property (times number of properties)	
1809	770	2809	385	Filing a submission after final rejection (37 CFR § 1.129(a))	
1810	770	2810	385	For each additional invention to be examined (37 CFR § 1.129(b))	
1801	770	2801	385	Request for Continued Examination (RCE)	
1802	900	1802	900	Request for expedited examination of a design application	
				Other fee (specify) ____	

*Reduced by Basic Filing Fee Paid

SUBTOTAL (3) ($) 130

SUBMITTED BY				Complete (if applicable)	
Name (Print/Type)	Ajay Pathak	Registration No. Attorney/Agent	38,266	Telephone	703-668-8000
Signature		#34,313		Date	July 16, 2004

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

Burden Hour Statement: This form is estimated to take 0.2 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Washington, DC 20231.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patent Application

Inventors: KATHLEEEN P. BARTON et al.

Docket No.: Pharmacia Ref. No. 003272/3/US
New HDP Ref. No. 6794A-000061/US/COG

Application No.: 10/727,681 (Continuation of 09/792,208) Group Art Unit: Unknown

Filing Date: December 4, 2003

Title: Eplerenone Crystal Form Exhibiting Enhanced Dissolution Rate

Examiner: Unknown

ASSOCIATE POWER OF ATTORNEY AND CHANGE OF ADDRESS

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

POWER OF ATTORNEY

Please grant associate power of attorney in the above-captioned application to the following attorney:

Ajay S. Pathak	Registration No. 38,266
Kenton N. Fedde	Registration No. 54,701
Philip B. Polster, II	Registration No. 43,864
Joseph R. Schuh	Registration No. 48,180
Patricia K. Fitzsimmons	Registration No. 52,894
Julie M. Lappin	Registration No. 46,612
Christopher W. Slavinsky	Registration No. 54,456

and add the attorneys of Customer No. 30593, including the following attorneys of Harness, Dickey & Pierce, P.L.C., to prosecute this application and to transact all business in the Patent and

Trademark Office connected therewith:

Terry L. Clark	Registration No. 32,644
Donald J. Daley	Registration No. 34,313
John A. Castellano	Registration No. 35,094
Gary D. Yacura	Registration No. 35,416
Thomas S. Auchterlonie	Registration No. 37,275
John E. Curtin	Registration No. 37,602
Gregory P. Brummett	Registration No. 41,646

CORRESPONDENCE ADDRESS

I request the Patent and Trademark Office to direct all correspondence and telephone calls relative to this application to Customer No. 30593, Harness, Dickey & Pierce, P.L.C., P.O. Box 8910, Reston, Virginia 20195, (703) 668-8000.

The undersigned is empowered with full Power of Attorney on behalf of the assignee.

Respectfully submitted,

Dated: 7/13/04

Scott A. Williams
Registration No. 39,876
Pharmacia Corporation
575 Maryville Center Drive
St. Louis, MO 63141
(314) 274-9090

C-3272/02

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Anticipated Classification of This Application: Class 540
Subclass
Prior Application: Examiner: BARBARA B. BADIO Art Unit 1616

COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Transmitted herewith for filing is a continuation under 37 C.F.R 1.53(b), of pending prior Application Serial Number 09/732,208 filed on December 7, 2000, of Kathleen P. Barton, Thomas B. Borchardt, Marlon V. Carlos, Subhash Desai, Leonard J. Ferro, Henry T. Gaud, Scott S. Ganser, Clay R. Little, Partha S. Mudipalli, Mark A. Pietz, Daniel R. Pilipauskas, Yuen-Lung L. Sing, Glenn L. Stahl, Joseph J. Wieczorek and Chris Y. Yan entitled **EPLERENONE CRYSTAL FORM EXHIBITING ENHANCED DISSOLUTION RATE.**

[X] Enclosed is a copy of the prior application, including the Oath of Declaration as originally filed December 7, 2000. I hereby verify that the attached papers are a true copy of said prior application as originally filed on December 7, 2000.

[ ] Cancel in this application, original Claims ___ of the prior application before calculating the filing fee. (At least one original, independent claim must be retained for filing purposes).

[X] Amend the specification by replacing the first paragraph with the following: -- This application is a continuation of prior U.S. Application Serial No. 09/732,208 filed December 7, 2000, which is a continuation-in-part of U.S. Application Serial No. 09/246,204 filed on February 8, 1999, which is a division of U.S. Application Serial No. 08/763,910 filed on December 11, 1996 (U.S. Patent No. 5,981,744), which claims priority of U.S. Provisional Application Serial No. 60/008,455 filed on December 11, 1995; --

[X] The filing fee is calculated below:

Basic Filing Fee [37 CFR 1.16(a)]				$750.00
Additional Filing Fee [37 CFR 1.16(b), (c)]				
Claims	No. Filed	No. Extra	Rate	
Independent	16 - 3 =	13	X $84.00 =	1092.00
Total	32 - 20 =	12	X $18.00 =	$216.00
				$2058.00
			TOTAL FEE:	

[X] A triplicate copy of this transmittal paper is enclosed.
[X] Please charge the above calculated total fee to Deposit Account No. 19-1025.
[X] The Commissioner is hereby authorized and requested to charge any fees for extensions of time and any other fees in addition to the above as well as all future fees set forth in 37 CFR 1.16 and 1.17 which may be required during the entire pendency of this Application, and credit any overcharges to

37 C.F.R. 1.53(b) APPLICATION
Continuation or Divisional
Page 2 of 2

C-3272/02

Deposit Account No. 19-1025 [37 CFR 1.25(b)].

NOTE: THIS AUTHORIZATION DOES NOT INCLUDE FEES REQUIRED UNDER 37 CFR 1.18

[X] Transfer the drawings from the prior application to this application and abandon said prior application as of the filing date accorded this application. ANOTHER DUPLICATE COPY OF THIS SHEET IS ENCLOSED FOR FILING IN THE PRIOR APPLICATION FILE.

[] New formal drawings are enclosed.

[] Priority of Application Serial No. _____, filed on _____ in _____ (country) is claimed under 35 U.S.C. 119.

[] The certified copy of the priority application has been filed in prior Application Serial No. _____, filed _____.

[X] The prior application is assigned of record to G.D. Searle & Co., P.O. Box 5110, Chicago, Illinois 60680.

[X] The Power of Attorney in the prior application is to James C. Forbes, Registration No. 39,457.

[X] The power appears in the original papers in the prior application.

[X] Enclosed is an Associate Power of Attorney from J. Timothy Keane to Joseph R. Schuh.

[X] Address all future communications to:

Joseph R. Schuh
PHARMACIA CORPORATION
of Pfizer Inc.
Corporate Patent Department
P.O. Box 1027
Chesterfield, MO 63006

The undersigned declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: December 4, 2003

Joseph R. Schuh

Joseph R. Schuh
Agent for Applicants
Registration No. 48,180
314-274-8182 (St. Louis)

Address of Signer:
Pharmacia Corporation
Mail Zone MC5
575 Maryville Centre Drive
St. Louis, MO 63141

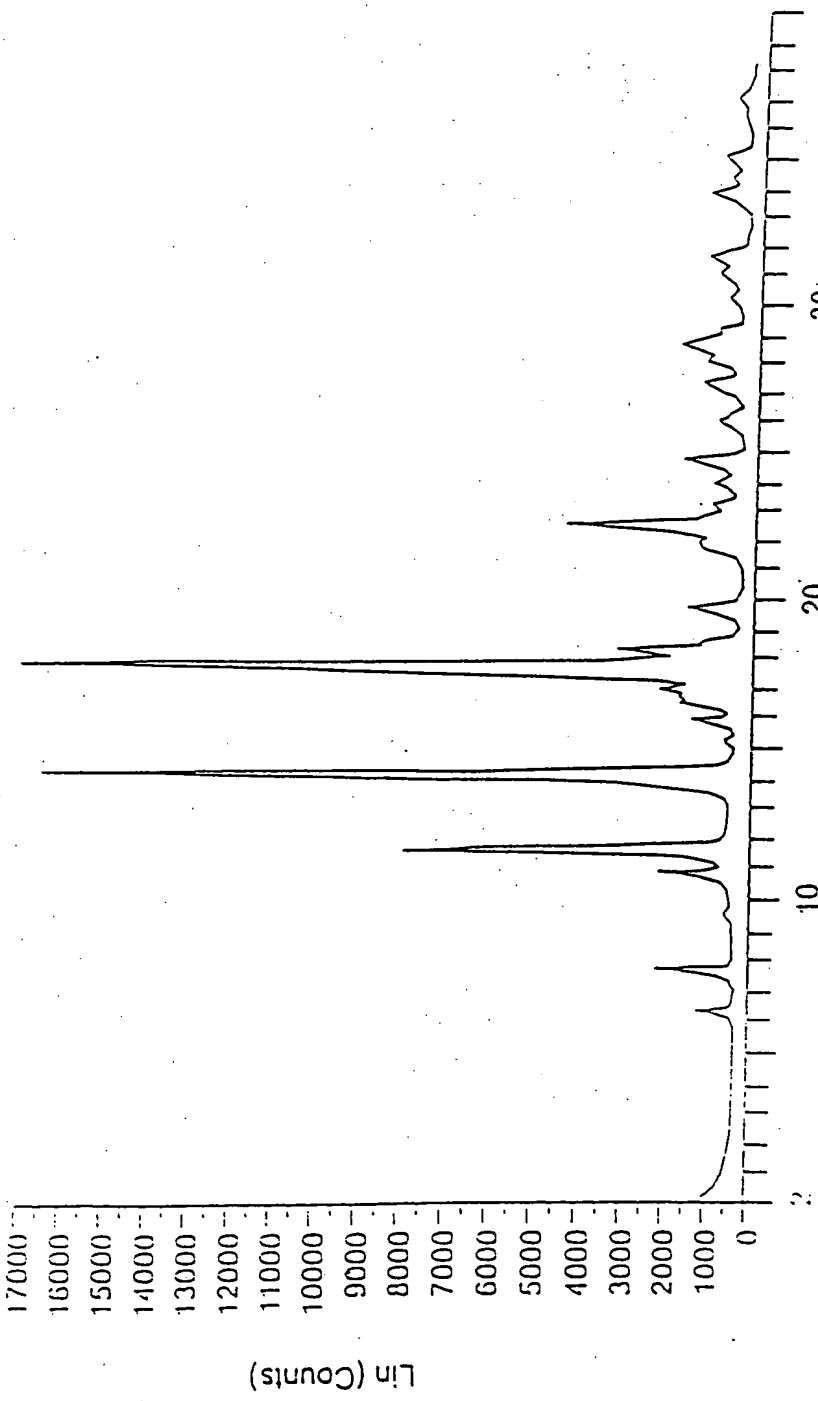


Fig. 1-A

APPLICATION FOR UNITED STATES PATENT
DECLARATION * POWER OF ATTORNEY * PETITION

AS A BELOW-NAMED INVENTOR, I/WE hereby declare that:

MY/OUR RESIDENCE, citizenship, and post office address are as stated below, next to my/our name.

I/WE BELIEVE I am/we are the original, first and joint inventor(s), of the subject matter which is claimed and for which a patent is sought on the invention entitled:

EPLERENONE CRYSTAL FORM

EXHIBITING ENHANCED DISSOLUTION RATE

the specification of which, with any Preliminary Amendment, was filed as United States Application Serial No. 09/732,208 on December 7, 2000.

I/WE HEREBY STATE that I/we have reviewed and understand the contents of the above-identified specifications including the claims, as amended by any Amendment(s) referred to above.

I/WE ACKNOWLEDGE the Duty to Disclose to the Patent and Trademark Office all information known to me/us to be material to patentability of the subject matter claimed in this application, as "materiality" is defined in Title 37, Code of Federal Regulations, § 1.56.

I/We hereby claim priority benefits under Title 35, United States Code, § 119 of any foreign application(s) for patent, United States provisional application(s), or inventor's certificate listed below and have also identified below any foreign application for patent, United States provisional application, or inventor's certificate having a filing date before that of the application on which priority is claimed:

			Priority Claimed
09/246,204	USA	February 8, 1999	Yes
08/763,910	USA	December 11, 1996	Yes
60/008,455	USA	December 11, 1995	Yes
09/246,908	USA	February 9, 1999	Yes
09/583,158	USA	May 30, 2000	Yes
09/583,137	USA	May 30, 2000	Yes
09/319,673	USA	December 13, 1999	Yes
60/049,388	USA	June 11, 1997	Yes
60/033,315	USA	December 11, 1996	Yes
60/169,556	USA	December 8, 1999	Yes
60/169,608	USA	December 8, 1999	Yes
60/169,639	USA	December 8, 1999	Yes
60/169,682	USA	December 8, 1999	Yes
60/169,690	USA	December 8, 1999	Yes
60/169,807	USA	December 8, 1999	Yes
(Serial No.)	(Country)	(Date Filed)	(Yes/No)

I/We hereby claim the benefit under Title 35, United States Code, § 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided

by the first paragraph of Title 35, United States Code, § 112, I/we acknowledge the duty to disclose all information known to me/us to be material to patentability of the subject matter claimed in this application, as "materiality" is defined in title 37, Code of Federal Regulations, § 1.56, which becomes available between the filing date of the prior application and the national or PCT international filing date of this application:

			Priority Claimed
PCT/US97/23090	USA	December 11, 1997	Yes
(Serial No.)	(Country)	(Date Filed)	(Yes/No)

I/We hereby appoint the following as my/our attorney(s) and/or agent(s) of record with full power of substitution and revocation to prosecute this Application and to transact all business in the Patent and Trademark Office connected therewith.

Christopher S. Bauer	**Reg. No. 42,305**
Dennis A. Bennett	**Reg. No. 34,547**
James C. Forbes	**Reg. No. 39,457**
J. Timothy Keane	**Reg. No. 27,808**
Verne A. Luckow	**Reg. No. 45,950**
Scott J. Meyer	**Reg. No. 25,275**
Richard A. Mueller	**Reg. No. 41,094**
Rachel A. Polster	**Reg. No. 47,004**
James M. Warner	**Reg. No. 45,199**
Scott A. Williams	**Reg. No. 39,876**

I/We hereby direct that all correspondence be addressed to:

Pharmacia Corporation
Patent Department Central - 1810
P.O. Box 5110
Chicago, IL 60680-5110

I/WE HEREBY DECLARE THAT ALL STATEMENTS MADE OF MY/OUR OWN KNOWLEDGE ARE TRUE AND THAT ALL STATEMENTS MADE ON INFORMATION AND BELIEF ARE BELIEVED TO BE TRUE; AND FURTHER THAT THESE STATEMENTS WERE MADE WITH THE KNOWLEDGE THAT WILLFUL FALSE STATEMENTS AND THE LIKE SO MADE ARE PUNISHABLE BY FINE OR IMPRISONMENT, OR BOTH, UNDER SECTION 1001 OF TITLE 18 OF THE UNITED STATES CODE AND THAT SUCH WILLFUL FALSE STATEMENTS MAY JEOPARDIZE THE VALIDITY OF THE APPLICATION OR ANY PATENT ISSUED THEREON.

WHEREFORE, I/WE PRAY that Letters Patent be granted to me/us solely or jointly with the additional inventor(s) named below for the invention described and claimed in the above-identified specification and claims, and I/we hereby subscribe my/our name to the above-identified specification and claims, Declaration, Power of Attorney and this Petition.

Inventor's Full Name:	KATHLEEN P. BARTON	
Inventor's Signature:	Kathleen P Barton	Date: 7-11-01
Country of Citizenship:	USA	
Residence Address:	813 Cherokee Road, Lake Forest, IL 60045	
Post Office Address: (if different from above)		

COPY

Inventor's Full Name:	THOMAS B. BORCHARDT	
Inventor's Signature:	Thomas B.	Date: 3/30/01
Country of Citizenship:	USA	
Residence Address:	8630 82nd Street, #107, Pleasant Prairie, WI 53158	
Post Office Address: (if different from above)		

Inventor's Full Name:	MARLON V. CARLOS	
Inventor's Signature:		Date: 7/11/01
Country of Citizenship:	USA	
Residence Address:	71 E. Fremont, Des Plaines, IL 60016	
Post Office Address: (if different from above)		

Inventor's Full Name:	SUBHASH DESAI	
Inventor's Signature:		Date:
Country of Citizenship:	USA	
Residence Address:	1011 Greenwood Avenue, Wilmette, IL	
Post Office Address: (if different from above)		

Inventor's Full Name:	LEONARD J. FERRO	
Inventor's Signature:	Leonard J. Ferro	Date: 30 Mar 2001
Country of Citizenship:	USA	
Residence Address:	3055 Priscilla Avenue, Highland Park, IL 60035	
Post Office Address: (if different from above)		

COPY

Inventor's Full Name:	HENRY T. GAUD	
Inventor's Signature:	Henry T. Gaud	Date: 7/11/1
Country of Citizenship:	USA	
Residence Address:	2809 Lincoln Street, Evanston, IL 60201	
Post Office Address: (if different from above)		

Inventor's Full Name:	SCOTT S. GANSER	
Inventor's Signature:	Scott S. Ganser	Date: 3-30-2001
Country of Citizenship:	USA	
Residence Address:	3312 Eighth Street, Park City, IL 60085	
Post Office Address: (if different from above)		

Inventor's Full Name:	CLAY R. LITTLE	
Inventor's Signature:	Clay R. Little	Date: 07/31/01
Country of Citizenship:	USA	
Residence Address:	2870 Farmington Drive, Lindenhurst, IL 60046	
Post Office Address: (if different from above)		

Inventor's Full Name:	PARTHA S. MUDIPALLI	
Inventor's Signature:	Partha S Mudipalli	Date: 07/11/01
Country of Citizenship:	~~USA~~ INDIA Any	
Residence Address:	4800 Carol Street, #1A, Skokie, IL 60077	
Post Office Address: (if different from above)		

COPY

Inventor's Full Name:	MARK A. PIETZ	
Inventor's Signature:	Mark A. Pietz	Date: 7/11/01
Country of Citizenship:	USA	
Residence Address:	182 Crisfield Drive, Grayslake, IL 60030	
Post Office Address: (if different from above)		

Inventor's Full Name:	DANIEL R. PILIPAUSKAS	
Inventor's Signature:	Daniel R. Pilipauskas	Date: 7/11/01
Country of Citizenship:	USA	
Residence Address:	317 Harlem, Glenview, IL 60025	
Post Office Address: (if different from above)		

Inventor's Full Name:	YUEN-LUNG L. SING	
Inventor's Signature:	Yuen-Lung Sing	Date: 7/12/01
Country of Citizenship:	USA	
Residence Address:	455 Hammermill Road, St. Louis, MO 63141	
Post Office Address: (if different from above)		

Inventor's Full Name:	GLENN L. STAHL	
Inventor's Signature:	Glenn L Stahl	Date: 7/11/01
Country of Citizenship:	USA	
Residence Address:	230 Cherrywood Road, Buffalo Grove, IL 60089	
Post Office Address: (if different from above)		

COPY

Inventor's Full Name:	JOSEPH J. WIECZOREK	
Inventor's Signature:	Joseph J Wieczorek	Date: 7/11/01
Country of Citizenship:	USA	
Residence Address:	504 Surrey Ridge Drive, Cary, IL 60013	
Post Office Address: (if different from above)		

Inventor's Full Name:	CHRIS Y. YAN	
Inventor's Signature:		Date:
Country of Citizenship:	USA	
Residence Address:	213 Arcadia Court, Vernon Hills, IL 60061	
Post Office Address: (if different from above)		

Inventor's Full Name:	KATHLEEN P. BARTON	
Inventor's Signature:		Date:
Country of Citizenship:	USA	
Residence Address:	813 Cherokee Road, Lake Forest, IL 60045	
Post Office Address: (if different from above)		

Inventor's Full Name:	THOMAS B. BORCHARDT	
Inventor's Signature:		Date:
Country of Citizenship:	USA	
Residence Address:	8630 82nd Street, #107, Pleasant Prairie, WI 53158	
Post Office Address: (if different from above)		

Inventor's Full Name:	MARLON V. CARLOS	
Inventor's Signature:		Date:
Country of Citizenship:	USA	
Residence Address:	71 E. Fremont, Des Plaines, IL 60016	
Post Office Address: (if different from above)		

Inventor's Full Name:	SUBHASH DESAI	
Inventor's Signature:	Subhash Desai	Date: 9/11/01
Country of Citizenship:	USA	
Residence Address:	1011 Greenwood Avenue, Wilmette, IL	
Post Office Address: (if different from above)		

Inventor's Full Name:	GLENN L. STAHL
Inventor's Signature:	Date:
Country of Citizenship:	USA
Residence Address:	230 Cherrywood Road, Buffalo Grove, IL 60089
Post Office Address: (if different from above)	

COPY

Inventor's Full Name:	JOSEPH J. WIECZOREK
Inventor's Signature:	Date:
Country of Citizenship:	USA
Residence Address:	504 Surrey Ridge Drive, Cary, IL 60013
Post Office Address: (if different from above)	

Inventor's Full Name:	CHRIS Y. YAN
Inventor's Signature:	Date: 8-15-01
Country of Citizenship:	~~USA~~ Canadian
Residence Address:	511 Ravens Crest Dr. E., Plainsboro, NJ 08536
Post Office Address: (if different from above)	

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371 (c) DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NUMBER
10/727,681	12/04/2003	Kathleen P. Barton	C-3272/1/US

Joseph R. Schuh
PHARMACIA CORPORATION of Pfizer Inc.
Corporate Patent Department
P. O. Box 1027
Chesterfield, MO 63006

CONFIRMATION NO. 8460

FORMALITIES LETTER

OC000000012696573

Date Mailed: 05/18/2004

NOTICE OF INCOMPLETE NONPROVISIONAL APPLICATION

FILED UNDER 37 CFR 1.53(b)

A filing date has NOT been accorded to the above-identified application papers for the reason(s) indicated below.

All of the items noted below **and a newly executed oath or declaration covering the items must** be submitted within **TWO MONTHS** of the date of this Notice, unless otherwise indicated, or proceedings on the application will be terminated *(37 CFR 1.53(e))*. Replies should be mailed to: Mail Stop Missing Parts, Commissioner for Patents, P.O. Box 1450, Alexandria VA 22313-1450.

The filing date will be the date of receipt of all items required below, unless otherwise indicated. Any assertions that the item(s) required below were submitted, or are not necessary for a filing date, must be by way of petition directed to the attention of the Office of Petitions accompanied by the $130.00 petition fee *(37 CFR 1.17(h))*. If the petition states that the application is entitled to a filing date, a request for a refund of the petition fee may be included in the petition. Petitions should be mailed to: Mail Stop Petitions, Commissioner for Patents, P.O. Box 1450, Alexandria VA 22313-1450.

- The application was deposited without drawings. 35 U.S.C. 113 (first sentence) requires a drawing "where necessary for the understanding of the subject matter sought to be patented." *Applicant should reconsider whether the drawings are necessary under 35 U.S.C. 113 (first sentence).*

The application is informal since it does not comply with the regulations for the reason(s) indicated below.

The required item(s) identified below must be timely submitted to avoid abandonment:

- A substitute specification in compliance with 37 CFR 1.52, 1.121(b)(3), and 1.125, is required. The specification, claims, or abstract page(s) submitted is not acceptable and cannot be scanned or properly stored because:

    - Papers must be legibly written either by a typewriter or mechanical printer in permanent ink or its equivalent in portrait orientation on flexible, strong, smooth, non-shiny, durable, and white paper. Application papers must be presented in a form having sufficient clarity and contrast between the paper and the writing thereon to permit the direct reproduction of readily legible copies in any number by use of photographic, electrostatic, photo-offset, and microfilming processes and electronic reproduction by use of digital imaging and optical character recognition. Pages 1-6,

10 ,21-28, 35, 41, 48-49, 52, 54, 59-60, 62, 64--66, 69 are not in compliance with 37 CFR 1.52(a).

COPY

Replies should be mailed to: Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

A copy of this notice MUST be returned with the reply.

Customer Service Center
Initial Patent Examination Division (703) 308-1202
PART 2 - COPY TO BE RETURNED WITH RESPONSE

C-3272/1/US

EPLERENONE CRYSTALLINE FORM EXHIBITING ENHANCED DISSOLUTION RATE

This application is a continuation-in-part of U.S. application Serial No. 09/246,204 filed on February 8, 1999, which is a division of U.S. application Serial No. 08/763,910 filed on December 11, 1996 (U.S. Patent No. 5,981,744), which claims priority of U.S. provisional application Serial No. 60/008,455 filed on December 11, 1995;

and is a continuation-in-part of U.S. application Serial No. 09/246,908 filed on February 9, 1999, which is a division of U.S. application Serial No. 08/763,910 filed on December 11, 1996 (U.S. Patent No. 5,981,744), which claims priority of U.S. provisional application Serial No. 60/008,455 filed on December 11, 1995;

and is a continuation-in-part of U.S. application Serial No. 09/583,158 filed on May 30, 2000, which is a division of U.S. application Serial No. 09/246,908 filed on February 9, 1999, which is a division of U.S. application Serial No. 08/763,910 filed on December 11, 1996 (U.S. Patent No. 5,981,744), which claims priority of U.S. provisional application Serial No. 60/008,455 filed on December 11, 1995;

and is a continuation-in-part of U.S. application Serial No. 09/583,137 filed on May 30, 2000, which is a division of U.S. application Serial No. 09/246,908 filed on February 9, 1999, which is a division of U.S. application Serial No. 08/763,910 filed on December 11, 1996 (U.S. Patent No. 5,981,744), which claims priority of U.S. provisional application Serial No. 60/008,455 filed on December 11, 1995;

and is a continuation-in-part of U.S. application Serial No. 09/319,673 filed on December 13, 1999, which is a national stage application filed under 35 U.S.C. §371 based on international application Serial No. PCT/US97/23090 filed on December 11, 1997, which claims priority of U.S. provisional application Serial No. 60/049,388 filed on June 11, 1997 and U.S. provisional application Serial No. 60/033,315 filed on December 11, 1996.

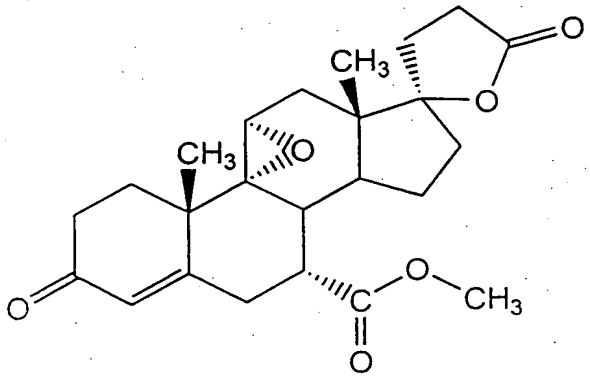
This application also claims priority of U.S. provisional application Serial No. 60/169,556, U.S. provisional application Serial No. 60/169,608, U.S. provisional application Serial No. 60/169,639, U.S. provisional application Serial No. 60/169,682, U.S. provisional application Serial No. 60/169,690, and U.S. provisional application Serial No. 60/169,807, all filed on December 8, 1999.

FIELD OF THE INVENTION

This invention is in the field of pharmaceutical agents active as aldosterone receptor antagonists, more particularly to the aldosterone receptor antagonist eplerenone. Specifically, the invention relates to a novel crystalline form of eplerenone, to methods of preparing this crystalline form, to pharmaceutical compositions comprising this crystalline form, to methods for treatment and/or prophylaxis of aldosterone-mediated conditions and/or disorders, including conditions and disorders associated with hyperaldosteronism such as hypertension, using this crystalline form, and to use of this crystalline form in manufacture of medicaments.

BACKGROUND OF THE INVENTION

The compound methyl hydrogen 9,11-epoxy-17-hydroxy-3-oxopregn-4-ene-7,21-dicarboxylate, γ-lactone having the structure (I) and known as eplerenone was first reported in U.S. Patent No. 4,559,332 to Grob *et al.*, which discloses a class of 9,11-epoxy steroid compounds and their salts. Eplerenone is an aldosterone receptor antagonist and can be administered in a therapeutically effective amount where use of an aldosterone receptor antagonist is indicated, such as in treatment of pathological conditions associated with hyperaldosteronism including hypertension, heart failure including cardiac insufficiency, and cirrhosis of the liver.



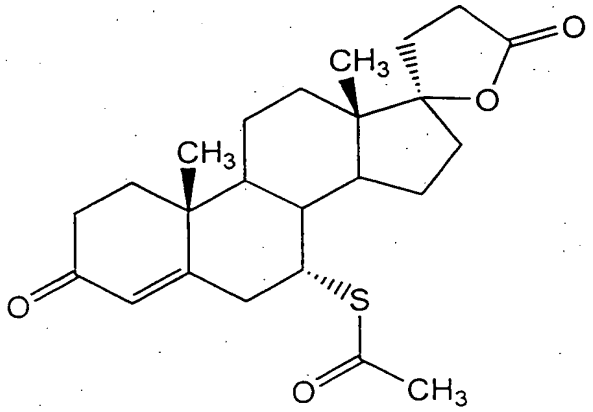
(I)

Above-cited U.S. Patent No. 4,559,332, which is incorporated herein by reference, generally discloses preparation of eplerenone and preparation of pharmaceutical compositions comprising eplerenone. Additional processes for the preparation of 9,11-epoxy steroid compounds and their salts, including eplerenone, are disclosed in International Patent Publications No. WO 97/21720 and No. WO 98/25948.

Grob *et al.* (1997), "Steroidal aldosterone antagonists: increased selectivity of 9α,11-epoxy derivatives", Helvetica Chimica Acta, 80, 566-585, discloses an X-ray crystal structure analysis of a solvate of eplerenone prepared by crystallizing eplerenone from a methylene chloride/diethyl ether solvent system.

De Gasparo *et al.* (1989), "Antialdosterones: incidence and prevention of sexual side effects", Journal of Steroid Biochemistry, 32(13), 223-227, discloses use of non-formulated eplerenone having a 20 μm particle size in a single dose study of eplerenone.

Spironolactone a 20-spiroxane-steroid of structure (II) having activity as an aldosterone receptor antagonist, is commercially available for treatment of hypertension. Spironolactone, however, has antiandrogenic activity that can result in gynecomastia and impotence in men. It also has weak progestational activity that can produce menstrual irregularities in women. Accordingly, there is interest in development of additional active aldosterone receptor antagonists such as eplerenone that do not interact with other steroid receptor systems such as glucocorticoid, progestin and androgen steroid receptor systems and/or that provide for a broader range of treatment.



(II)

Agafonov *et al.* (1991), "Polymorphism of spironolactone", Journal of Pharmaceutical Sciences, 80(2), 181-185, discloses an acetonitrile solvate, an ethanol solvate, an ethyl acetate solvate, a methanol solvate and two non-solvated polymorphic crystalline forms of spironolactone. Brittan (1999), Polymorphism in Pharmaceutical Solids, pp. 114-116, 207, 235 and 261 (Marcel Dekker), likewise discloses these solid state forms of spironolactone.

Eplerenone has very low solubility in aqueous media and release of the drug in the gastrointestinal tract from oral dosage forms is often a limiting factor to bioavailability of the drug, and more particularly to speed of onset of therapeutic effect following oral administration.

SUMMARY OF THE INVENTION

There is now provided a novel crystalline form of eplerenone having a relatively rapid dissolution rate in aqueous media and having other unique properties relative to other solid state forms of eplerenone. This crystalline form is fully characterized hereinbelow but is referred to for convenience as "Form H".

The invention provides, in a first aspect, this novel crystalline Form H of eplerenone *per se*. Among the properties distinguishing Form H from another crystalline form, referred to as "Form L", Form H exhibits an orthorhombic crystal system, an X-ray powder diffraction pattern with a peak at 12.0 ± 0.2 degrees 2θ and a melting point in a range from about 247°C to about 251°C.

In a second aspect, the invention provides an eplerenone drug substance comprising Form H eplerenone in at least a detectable amount.

In a third aspect, the invention provides an eplerenone drug substance that is substantially phase pure Form H eplerenone. The term "phase pure" herein refers to purity with respect to other solid state forms of eplerenone and does not necessarily imply a high degree of chemical purity with respect to other compounds.

In a fourth aspect, the invention provides solvated crystalline forms of eplerenone that, when desolvated, can yield Form H eplerenone.

In a fifth aspect, the invention provides pharmaceutical compositions comprising Form H eplerenone, optionally accompanied by one or more other solid state forms of eplerenone, in a total unit dosage amount of eplerenone of about 10 to about 1000 mg, and further comprising one or more pharmaceutically acceptable excipients.

In a sixth aspect, the invention provides processes for preparing Form H eplerenone and for preparing compositions comprising Form H eplerenone.

In a seventh aspect, the invention provides a method for prophylaxis and/or treatment of an aldosterone-mediated condition or disorder comprising administering to a subject a therapeutically effective amount of eplerenone, wherein at least a

fraction of the eplerenone present is Form H eplerenone.

Additional aspects of the invention are discussed throughout the specification of this application.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1-A shows X-ray powder diffraction patterns of Form H eplerenone.

Fig. 1-B shows X-ray powder diffraction patterns of Form L eplerenone.

Fig. 1-C shows X-ray powder diffraction patterns of the methyl ethyl ketone solvate of eplerenone.

Figs. 1-D through 1-O show X-ray powder diffraction patterns of the following eplerenone solvates: n-propyl alcohol, tetrahydrofuran, ethyl propionate, acetic acid, acetone, toluene, isopropanol, ethanol, isobutyl acetate, butyl acetate, methyl acetate and propyl acetate solvates respectively.

Fig. 2-A shows a differential scanning calorimetry (DSC) thermogram of non-milled Form L eplerenone directly crystallized from methyl ethyl ketone.

Fig. 2-B shows a DSC thermogram of non-milled Form L eplerenone prepared by desolvation of a solvate obtained by crystallization of a high purity eplerenone from methyl ethyl ketone.

Fig. 2-C shows a DSC thermogram of Form L eplerenone prepared by milling the product of desolvation of a solvate obtained by crystallization of a high purity eplerenone from methyl ethyl ketone.

Fig. 2-D shows a DSC thermogram of non-milled Form H eplerenone prepared by desolvation of a solvate obtained by digestion of low purity eplerenone from appropriate solvents.

Figs. 2-E through 2-T show DSC thermograms for the following eplerenone solvates: n-propyl alcohol, tetrahydrofuran, ethyl propionate, acetic acid, chloroform, acetone, toluene, isopropanol, t-butyl acetate, ethanol, isobutyl acetate, butyl acetate, methyl acetate, propyl acetate, n-butanol and n-octanol solvates respectively.

Fig. 3-A shows infrared (IR) spectra (diffuse reflectance, DRIFT) of Form H eplerenone.

Fig. 3-B shows IR spectra (diffuse reflectance, DRIFT) of Form L eplerenone.

Fig. 3-C shows IR spectra (diffuse reflectance, DRIFT) of the methyl ethyl ketone solvate of eplerenone.

Fig. 3-D shows IR spectra (diffuse reflectance, DRIFT) of eplerenone in chloroform solution.

Figs. 3-E through 3-R show IR spectra for the following eplerenone solvates: n-propyl alcohol, tetrahydrofuran, ethyl propionate, acetic acid, acetone, toluene, isopropanol, ethanol, isobutyl acetate, butyl acetate, propyl acetate, methyl acetate, propylene glycol and t-butyl acetate solvates respectively.

Fig. 4 shows ^{13}C NMR spectra of Form H eplerenone.

Fig. 5 shows ^{13}C NMR spectra of Form L eplerenone.

Figs. 6-A through 6-R show thermogravimetric analysis profiles of the following eplerenone solvates: methyl ethyl ketone, n-propyl alcohol, tetrahydrofuran, ethyl propionate, acetic acid, chloroform, acetone, toluene, isopropanol, ethanol, isobutyl acetate, butyl acetate, methyl acetate, propyl acetate, propylene glycol, n-butanol, n-octanol and t-butyl acetate solvates respectively.

Fig. 7 is a scanning electron micrograph of Form L eplerenone prepared by desolvation of the methyl ethyl ketone solvate of eplerenone.

Fig. 8 is a scanning electron micrograph of Form L eplerenone prepared by direct crystallization from ethyl acetate.

Fig. 9 shows an X-ray powder diffraction pattern of a crystalline form of 7-methyl hydrogen 4α,5α;9α,11α-diepoxy-17 hydroxy-3-oxo-17α-pregnane-7α,21-dicarboxylate, γ-lactone (the "diepoxide") isolated from methyl ethyl ketone.

Fig. 10 shows an X-ray powder diffraction pattern of a crystalline form of 7-methyl hydrogen 11α,12α-epoxy-17-hydroxy-3-oxo-17α-pregn-4-ene-7α,21-dicarboxylate, γ-lactone (the "11,12-epoxide") isolated from isopropanol.

Fig. 11 shows an X-ray powder diffraction pattern of a crystalline form of 7-methyl hydrogen 17-hydroxy-3-oxo-17α-pregna-4,9(11)-diene-7α,21-dicarboxylate, γ-lactone (the "9,11-olefin") isolated from n-butanol.

Fig. 12 illustrates the relationship between Gibbs free energy and temperature for enantiotropically related polymorphs.

Fig. 13 shows X-ray powder diffraction patterns of methyl ethyl ketone solvate wet cake obtained from (a) 0%, (b) 1%, (c) 3% and (d) 5% diepoxide-doped methyl ethyl ketone crystallizations.

Fig. 14 shows X-ray powder diffraction patterns for dried solids obtained from

crystalline forms useful in directly preparing such compositions do not comprise methylene chloride, isopropanol or ethyl ether; in another embodiment, do not comprise methylene chloride, isopropanol, ethyl ether, methyl ethyl ketone or ethanol; and, in yet another embodiment, do not comprise methylene chloride, isopropanol, ethyl ether, methyl ethyl ketone, ethanol, ethyl acetate or acetone. Most preferably for this use, the solvated crystalline forms of eplerenone are substantially exclusive of solvents that are not pharmaceutically acceptable solvents.

Solvated crystalline forms used in pharmaceutical compositions generally and preferably comprise a pharmaceutically acceptable higher boiling point and/or hydrogen-bonding solvent such as, but not limited to, butanol. It is believed that the solvated crystalline forms collectively can offer a range of different dissolution rates and, where dissolution of eplerenone in the gastrointestinal tract is the rate-controlling step for delivery of the eplerenone to the target cells or tissues, a range of different bioavailabilities relative to Form H and Form L.

The invention also relates to an amorphous form of eplerenone. Amorphous eplerenone is useful as an intermediate in the preparation of Form H and Form L eplerenone. In addition, it is believed that amorphous eplerenone possesses a different dissolution rate and, where amorphous eplerenone is present in a pharmaceutical composition and where dissolution of eplerenone in the gastrointestinal tract is the rate-controlling step for delivery of the eplerenone to the target cells, such amorphous eplerenone can provide different bioavailability relative to Form H and Form L.

Also of interest are combinations of solid state forms selected from the group consisting of Form H eplerenone, Form L eplerenone, solvated crystalline forms of eplerenone and amorphous eplerenone. Such combinations are useful, for example, in preparation of pharmaceutical compositions having a variety of dissolution profiles, including controlled-release compositions. In an embodiment of the present invention, a combination of solid state forms is provided comprising Form H eplerenone in at least a detectable amount, with the balance being one or more solid state forms selected from the group consisting of Form L eplerenone, solvated crystalline forms of eplerenone and amorphous eplerenone.

Depending upon the intended use of the solid state form of eplerenone, processing considerations may favor selection of a specific solid state form or a

at a rate of about 10°C/minute.

Examples of thermogravimetry analysis profiles are shown in Figs. 6-A through 6-R for the following solvated crystalline forms of eplerenone: methyl ethyl ketone solvate, n-propyl alcohol solvate, tetrahydrofuran solvate, ethyl propionate solvate, acetic acid solvate, chloroform solvate, acetone solvate, toluene solvate, isopropanol solvate, ethanol solvate, isobutyl acetate solvate, butyl acetate solvate, methyl acetate solvate, propyl acetate solvate, propylene glycol solvate, n-butanol solvate, n-octanol solvate, and t-butyl acetate solvate, respectively.

7. Microscopy

Hot-stage microscopy was performed on single crystals of the methyl ethyl ketone solvate of eplerenone using a Linkam THMS 600 Hot Stage with Zeiss Universal Polarized Light Microscope. Under polarized light at room temperature the solvate crystal was birefringent and translucent indicating that the crystal lattice was highly ordered. As the temperature increased to about 60°C, noticeable defects began to emerge along the long crystal dimension. A scanning electron micrograph of Form L eplerenone obtained by desolvation of the methyl ethyl ketone solvate is shown in Fig. 7 and reveals surface defects, pores, cracks and fractures within the crystal lattice. A scanning electron micrograph of Form L eplerenone obtained by direct crystallization from ethyl acetate is shown in Fig. 8 and does not exhibit similar surface defects, pores, cracks and fractures within the crystal lattice.

8. Unit cell parameters

Tables 3A, 3B and 3C below summarize the unit cell parameters determined for Form H, Form L, and several solvated crystalline forms of eplerenone.

Table 3A: Unit cell parameters for eplerenone crystal forms

Parameter	**Form H**	**Form L**	**Methyl ethyl ketone solvate**
Crystal system	Orthorhombic	Monoclinic	Orthorhombic
Space group	$P2_12_12_1$	$P2_1$	$P2_12_12_1$
a	21.22 Å	8.78 Å	23.53 Å
b	15.40 Å	11.14 Å	8.16 Å
c	6.34 Å	11.06 Å	13.08 Å
α	90°	90°	90°
β	90°	93.52°	90°
γ	90°	90°	90°

Parameter	Form H	Form L	Methyl ethyl – ketone solvate
Z	4	2	4
Volume (Å)	2071.3	1081.8	2511.4
ρ (calculated)	1.329 g/cm^3	1.275 g/cm^3	1.287 g/cm^3
R	0.0667	0.062	0.088

Table 3B: Unit cell parameters for eplerenone crystal forms

Parameter	Acetone solvate	Toluene solvate	Butyl acetate solvate[1]
Crystal system	Orthorhombic	Orthorhombic	Orthorhombic
Space group	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$
a	23.31 Å	23.64 Å	23.07 Å
b	13.13 Å	13.46 Å	13.10 Å
c	8.28 Å	8.16 Å	8.24 Å
α	90°	90°	90°
β	90°	90°	90°
γ	90°	90°	90°
Z	4	4	4
Volume (Å)	2533.7	2596.6	2490.0
ρ (calculated)	1.239 g/cm^3	1.296 g/cm^3	1.334 g/cm^3
R	0.058	0.089	0.093

[1]The butyl acetate solvate molecules were not completely refined due to disorder of the solvent molecules in the channels.

Table 3C: Unit cell parameters for eplerenone crystal forms

Parameter	Isobutyl acetate solvate[1]	Isopropanol solvate[1]	Ethanol solvate[1]
Crystal system	Orthorhombic	Orthorhombic	Orthorhombic
Space group	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$
a	23.19 Å	23.15 Å	23.51 Å
b	12.95 Å	12.73 Å	13.11 Å
c	8.25 Å	8.25 Å	8.27 Å
α	90°	90°	90°
β	90°	90°	90°
γ	90°	90°	90°
Z	4	4	4
Volume (Å)	2476.4	2433.2	2548.6
ρ (calculated)	1.337 g/cm^3	1.296 g/cm^3	1.234 g/cm^3
R	0.098	0.152	0.067

[1]The solvate molecules were not completely refined due to disorder of the solvent molecules in the channels.

Additional information on selected solvated crystalline forms of eplerenone is reported in Table 4 below. The unit cell data reported in Table 3A above for the methyl ethyl ketone solvate also are representative of the unit cell parameters for many of these additional eplerenone crystalline solvates. Most of the eplerenone crystalline solvates tested are substantially isostructural to each other. While there may be some minor shifting in the X-ray powder diffraction peaks from one solvated crystalline form to the next due to the size of the incorporated solvent molecule, the overall diffraction patterns are substantially the same and the unit cell parameters and molecular positions are substantially identical for most of the solvates tested.

Table 4: Additional information on eplerenone solvates

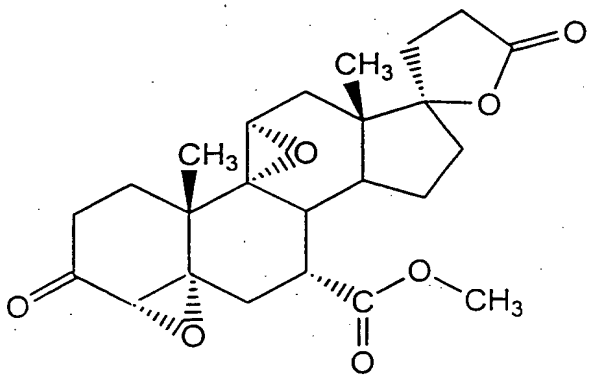
Solvent	Stoichiometry solvent: eplerenone	Isostructural to methyl ethyl ketone solvate?	Desolvation temperature[1] (°C)
Methyl ethyl ketone	1:1		89
Acetic acid	1:2	yes	203
Acetone	1:1	yes	117
Methyl acetate	1:1	yes	103
Propyl acetate	1:1	yes	130
Butyl acetate	1:2	yes	108
Isobutyl acetate	1:2	yes	112
t-Butyl acetate	---	yes	109
Chloroform	---	yes	125
Ethanol	1:1	yes	166
n-Propanol	1:1	yes	129
Isopropanol	1:1	yes	121
n-Butanol	1:1	yes	103
n-Octanol	---	yes	116
Ethyl propionate	1:1	yes	122
Propylene glycol	---	yes	188
Tetrahydrofuran	1:1	yes	136
Toluene	1:1	yes	83

[1]Defined as the extrapolated desolvation temperature from the final solvent weight loss step as determined by thermogravimetric analysis at a heating rate of 10°C/minute under nitrogen purge. Desolvation temperatures, however, can be affected by the method of manufacture of the solvate. Different methods can produce different numbers of nucleation sites capable of initiating desolvation in the solvate at lower temperatures.

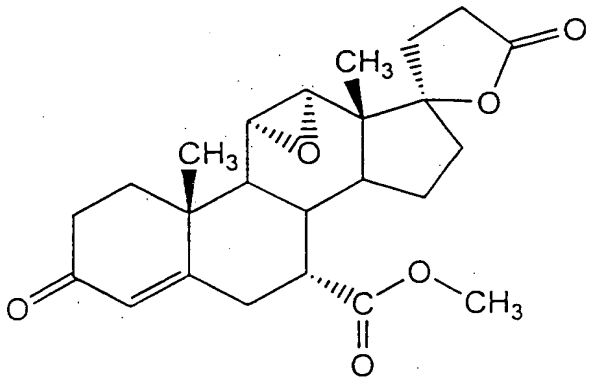
The unit cell of the solvate is composed of four eplerenone molecules. The stoichiometry of the eplerenone molecules and solvent molecules in the unit cell is also reported in Table 4 above for a number of solvates. The unit cell of Form H is composed of four eplerenone molecules. The unit cell of Form L is composed of two eplerenone molecules. The solvate unit cells are converted during desolvation into Form H and/or Form L unit cells when the eplerenone molecules undergo translation and rotation to fill the spaces left by the solvent molecules. Table 4 also reports the desolvation temperatures for a number of different solvates.

9. Crystal properties of impurities

Selected impurities in eplerenone can induce the formation of Form H during desolvation of a solvate. In particular, the effect of the following two impurity molecules was evaluated: 7-methyl hydrogen 4α,5α;9α,11α-diepoxy-17 hydroxy-3-oxo-17α-pregnane-7α,21-dicarboxylate, γ-lactone (III) (the "diepoxide"); and 7-methyl hydrogen 11α,12α-epoxy-17-hydroxy-3-oxo-17α-pregn-4-ene-7α,21-dicarboxylate, γ-lactone (IV) (the "11,12-epoxide").



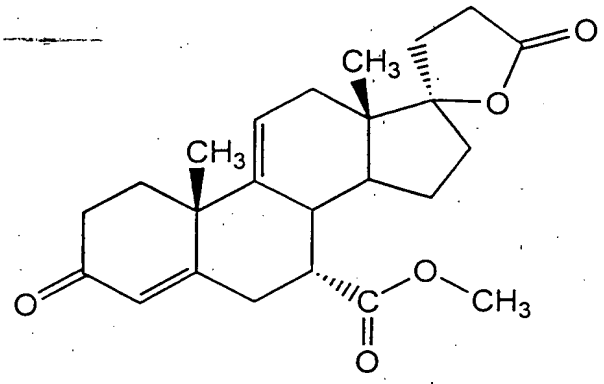
(III)



(IV)

The effect of these impurities on the eplerenone crystalline form resulting from desolvation is described in greater detail in the Examples herein.

Given the similarity in single crystal structure of 7-methyl hydrogen 17-hydroxy-3-oxo-17α-pregna-4,9(11)-diene-7α,21-dicarboxylate, γ-lactone (V) (the "9,11-olefin") and Form H eplerenone, it is hypothesized that the 9,11-olefin also can induce the formation of Form H during the desolvation of the solvate.



(V)

A single crystal form was isolated for each impurity compound. Representative X-ray powder diffraction patterns for the crystal forms isolated for the diepoxide, 11,12-epoxide and 9,11-olefin are given in Figs. 9, 10 and 11, respectively. The X-ray powder diffraction pattern of each impurity molecule is similar to the X-ray powder diffraction pattern of Form H, suggesting that Form H and the three impurity compounds have similar single crystal structures.

Single crystals of each impurity compound also were isolated and subjected to X-ray structure determination to verify that these three compounds adopt single crystal structures similar to that of Form H. Single crystals of the diepoxide were isolated from methyl ethyl ketone. Single crystals of the 11,12-epoxide were isolated from isopropanol. Single crystals of the 9,11-olefin were isolated from n-butanol. Crystal structure data determined for the crystalline form of each impurity compound are given in Table 5. The resulting crystal system and cell parameters were substantially the same for the Form H, diepoxide, 11,12-epoxide, and 9,11-olefin crystalline forms.

Table 5: Unit cell parameters for crystals of impurities by comparison with Form H eplerenone

Parameter	Form H	Diepoxide	11,12-epoxide	9,11-olefin
Crystal system	Orthorhombic	Orthorhombic	Orthorhombic	Orthorhombic
Space group	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$
a	21.22 Å	21.328 Å	20.90 Å	20.90 Å
b	15.40 Å	16.16 Å	15.55 Å	15.74 Å
c	6.34 Å	6.15 Å	6.38 Å	6.29 Å

Parameter	Form H	Diepoxide	11,12-epoxide	9,11-olefin
α	90°	90°	90°	90°
β	90°	90°	90°	90°
γ	90°	90°	90°	90°
Z	4	4	4	4
Volume (Å)	2071.3	2119.0	2073.2	2069.3
ρ (calculated)	1.329 g/cm^3	1.349 g/cm^3	1.328 g/cm^3	1.279 g/cm^3
R	0.0667	0.0762	0.0865	0.0764

The four compounds reported in Table 5 crystallize into the same space group and have similar cell parameters (*i.e.*, they are isostructural). It is hypothesized that the diepoxide, 11,12-epoxide and 9,11-olefin adopt a Form H conformation. The relative ease of isolation of a Form H packing (directly from solution) for each impurity compound indicates that the Form H lattice is a stable packing mode for this series of structurally similar compounds. It is contemplated that any compound that is substantially crystallographically isostructural to Form H eplerenone can be useful as a dopant in crystallizing Form H eplerenone from solution.

Accordingly, in a particular embodiment, there is provided a method for promoting crystallization of Form H eplerenone from a solution of eplerenone in a solvent or mixture of solvents, the method comprising doping the solution prior to crystallization with an effective amount of a compound that is crystallographically substantially isostructural to Form H eplerenone. It is to be understood that "doping" herein can be active, *i.e.*, deliberate addition of the doping compound to the solution, or passive, *i.e.*, arising from the presence of the doping compound as an impurity in the solution.

Preferred doping compounds according to this embodiment are the diepoxide, the 11,12-epoxide, and the 9,11-olefin, *i.e.*, compounds (III), (IV) and (V) respectively, above.

Preparation of eplerenone

The eplerenone starting material used to prepare the novel crystalline forms of the present invention can be prepared by methods known *per se*, including the methods set forth in above-cited International Patent Publications No. WO 97/21720 and No. WO 98/25948, particularly scheme 1 set forth in each of these publications.

Preparation of crystalline forms

1. Preparation of solvated crystalline form

The solvated crystalline forms of eplerenone can be prepared by crystallization of eplerenone from a suitable solvent or a mixture of suitable solvents. A suitable solvent or mixture of suitable solvents generally comprises an organic solvent or a mixture of organic solvents that solubilizes the eplerenone together with any impurities at an elevated temperature, but upon cooling, preferentially crystallizes the solvate. The solubility of eplerenone in such solvents or mixtures of solvents generally is about 5 to about 200 mg/ml at room temperature. The solvent or mixtures of solvents preferably are selected from those solvents previously used in the process to prepare the eplerenone starting material, particularly those solvents that would be pharmaceutically acceptable if contained in the final pharmaceutical composition comprising the eplerenone crystalline form. For example, a solvent system comprising methylene chloride that yields a solvate comprising methylene chloride generally is not desirable.

Each solvent used preferably is a pharmaceutically acceptable solvent, particularly a Class 2 or Class 3 solvent as defined in "Impurities: guideline for residual solvents", International Conference On Harmonisation Of Technical Requirements For Registration Of Pharmaceuticals For Human Use (recommended for adoption at Step 4 of the ICH Process on July 17, 1997 by the ICH Steering Committee). Still more preferably, the solvent or mixture of solvents is selected from the group consisting of methyl ethyl ketone, 1-propanol, 2-pentanone, acetic acid, acetone, butyl acetate, chloroform, ethanol, isobutanol, isobutyl acetate, methyl acetate, ethyl propionate, n-butanol, n-octanol, isopropanol, propyl acetate, propylene glycol, t-butanol, tetrahydrofuran, toluene, methanol and t-butyl acetate. Still more preferably, the solvent is selected from the group consisting of methyl ethyl ketone and ethanol.

In another embodiment of this process, the solvent or mixture of solvents is selected from the group consisting of 1-propanol, 2-pentanone, acetic acid, acetone, butyl acetate, chloroform, isobutanol, isobutyl acetate, methyl acetate, ethyl propionate, n-butanol, n-octanol, propyl acetate, propylene glycol, t-butanol, tetrahydrofuran, toluene, methanol and t-butyl acetate.

In another embodiment of this process, the solvent or mixture of solvents is selected from the group consisting of 1-propanol, 2-pentanone, acetic acid, acetone, butyl acetate, chloroform, isobutanol, isobutyl acetate, methyl acetate, ethyl propionate, n-butanol, n-octanol, n-propanol, propyl acetate, propylene glycol, t-butanol, tetrahydrofuran, toluene, methanol and t-butyl acetate.

To prepare the solvated crystalline form of eplerenone, an amount of the eplerenone starting material is solubilized in a volume of the solvent and cooled until crystals form. The solvent temperature at which the eplerenone is added to the solvent generally will be selected based upon the solubility curve of the solvent or mixture of solvents. For most of the solvents described herein, for example, this solvent temperature typically is at least about 25°C, preferably from about 30°C to the boiling point of the solvent, and more preferably from about 25°C below the boiling point of the solvent to the boiling point of the solvent.

Alternatively, hot solvent may be added to the eplerenone and the mixture can be cooled until crystals form. The solvent temperature at the time it is added to the eplerenone generally will be selected based upon the solubility curve of the solvent or mixture of solvents. For most of the solvents described herein, for example, the solvent temperature typically is at least 25°C, preferably from about 50°C to the boiling point of the solvent, and more preferably from about 15°C below the boiling point of the solvent to the boiling point of the solvent.

The amount of the eplerenone starting material mixed with a given volume of solvent likewise will depend upon the solubility curve of the solvent or mixture of solvents. Typically, the amount of eplerenone added to the solvent will not completely solubilize in that volume of solvent at room temperature. For most of the solvents described herein, for example, the amount of eplerenone starting material mixed with a given volume of solvent usually is at least about 1.5 to about 4.0 times, preferably about 2.0 to about 3.5 times, and more preferably about 2.5 times, the amount of eplerenone that will solubilize in that volume of solvent at room temperature.

After the eplerenone starting material has completely solubilized in the solvent, the solution typically is cooled slowly to crystallize the solvated crystalline form of eplerenone. For most of the solvents described herein, for example, the

least about 90% pure, still more preferably at least about 98% pure, and most preferably at least about 99% pure.

After the eplerenone starting material has completely dissolved in the solvent, the solution typically is cooled slowly to crystallize Form L eplerenone. For most of the solvents described herein, for example, the solution is cooled at a rate slower than about 1°C/minute, preferably at a rate of about 0.2°C/minute or slower, and more preferably at a rate of about 0.05°C/minute to about 0.1°C/minute.

The endpoint temperature at which the Form L crystals are harvested will depend upon the solubility curve of the solvent or mixture of solvents. For most of the solvents described herein, the endpoint temperature typically is less than about 25°C, preferably less than about 5°C, and more preferably less than about –5°C.

Alternatively, other techniques can be used to prepare Form L eplerenone crystals. Examples of such techniques include, but are not limited to, (i) dissolving the eplerenone starting material in one solvent and adding a co-solvent to aid in crystallization of Form L eplerenone, (ii) vapor diffusion growth of Form L eplerenone, (iii) isolation of Form L eplerenone by evaporation, such as rotary evaporation, and (iv) slurry conversion.

Crystals of Form L eplerenone prepared as described above can be separated from the solvent by any suitable conventional means such as by filtration or centrifugation.

In addition, Form L eplerenone can be prepared by digesting (as described below) a slurry of high purity eplerenone in methyl ethyl ketone and filtering the digested eplerenone at the boiling point of the slurry.

6. Preparation of Form H directly from solution

It is hypothesized that if crystallization is performed above the enantiotropic transition temperature (T_t) for Form H and Form L, particularly if Form H growth promoters or Form L growth inhibitors are present or the solvent is seeded with phase pure Form H crystals, Form H will crystallize directly from solution since Form H is more stable at these higher temperatures. The solvent system used preferably comprises a high boiling solvent such as nitrobenzene. Suitable Form H growth promoters include, but are not limited to, the diepoxide and 11,12-olefin compounds defined hereinabove.

is about 500 nm to about 1 μm.

Solid state forms of eplerenone having a D_{90} particle size less than about 15 μm can be prepared in accordance with applicable particle size reduction techniques known in the art. Such techniques include, but are not limited to, those described in the following patents and publications, each of which is incorporated herein by reference.

U.S. Patent No. 4,826,689 to Violanto & Fischer.
U.S. Patent No. 5,145,684 to Liversidge *et al.*
U.S. Patent No. 5,298,262 to Na & Rajagopalan.
U.S. Patent No. 5,302,401 to Liversidge *et al.*
U.S. Patent No. 5,336,507 to Na & Rajagopalan.
U.S. Patent No. 5,340,564 to Illig & Sarpotdar.
U.S. Patent No. 5,346,702 to Na & Rajagopalan.
U.S. Patent No. 5,352,459 to Hollister *et al.*
U.S. Patent No. 5,354,560 to Lovrecich.
U.S. Patent No. 5,384,124 to Courteille *et al.*
U.S. Patent No. 5,429,824 to June.
U.S. Patent No. 5,503,723 to Ruddy *et al.*
U.S. Patent No. 5,510,118 to Bosch *et al.*
U.S. Patent No. 5,518,187 to Bruno *et al.*
U.S. Patent No. 5,518,738 to Eickhoff *et al.*
U.S. Patent No. 5,534,270 to De Castro.
U.S. Patent No. 5,536,508 to Canal *et al.*
U.S. Patent No. 5,552,160 to Liversidge *et al.*
U.S. Patent No. 5,560,931 to Eickhoff *et al.*
U.S. Patent No. 5,560,932 to Bagchi *et al.*
U.S. Patent No. 5,565,188 to Wong *et al.*
U.S. Patent No. 5,569,448 to Wong *et al.*
U.S. Patent No. 5,571,536 to Eickhoff *et al.*
U.S. Patent No. 5,573,783 to Desieno & Stetsko.
U.S. Patent No. 5,580,579 to Ruddy *et al.*
U.S. Patent No. 5,585,108 to Ruddy *et al.*

1.5. Lubricants, glidants and anti-adherents

Compositions of the invention optionally comprise one or more pharmaceutically acceptable lubricants and/or glidants as excipients. Suitable lubricants and/or glidants include, either individually or in combination, glyceryl behapate (*e.g.*, Compritol™ 888); stearic acid and salts thereof, including magnesium, calcium and sodium stearates; hydrogenated vegetable oils (*e.g.*, Sterotex™); colloidal silica; talc; waxes; boric acid; sodium benzoate; sodium acetate; sodium fumarate; sodium chloride; DL-leucine; polyethylene glycols (*e.g.*, Carbowax™ 4000 and Carbowax™ 6000); sodium oleate; sodium lauryl sulfate; and magnesium lauryl sulfate. Such lubricants and/or glidants, if present, constitute in total about 0.1% to about 10%, preferably about 0.2% to about 8%, and more preferably about 0.25% to about 5%, of the total weight of the composition.

Magnesium stearate is a preferred lubricant used, for example, to reduce friction between the equipment and granulated mixture during compression of tablet formulations.

Suitable anti-adherents include talc, cornstarch, DL-leucine, sodium lauryl sulfate and metallic stearates. Talc is a preferred anti-adherent or glidant used, for example, to reduce formulation sticking to equipment surfaces and also to reduce static in the blend. Talc, if present, constitutes about 0.1% to about 10%, more preferably about 0.25% to about 5%, and still more preferably about 0.5% to about 2%, of the total weight of the composition.

1.6. Other excipients

Other excipients such as colorants, flavors and sweeteners are known in the pharmaceutical art and can be used in compositions of the present invention. Tablets can be coated, for example with an enteric coating, or uncoated. Compositions of the invention can further comprise, for example, buffering agents.

1.7. Preferred oral compositions

In one embodiment, a composition of the present invention comprises eplerenone in a desired amount and one or more cellulosic excipients. The term "cellulosic excipient" embraces excipients comprising cellulose or a derivative thereof, including without restriction purified cellulose, microcrystalline cellulose, and

alkylcelluloses and their derivatives and salts (*e.g.*, methylcellulose, ethylcellulose, hydroxypropylcellulose, HPMC, carboxymethylcellulose, sodium carboxymethylcellulose including croscarmellose sodium, *etc.*). Preferably, at least one such cellulosic excipient present is selected from the group consisting of (C_{1-6} alkyl)celluloses and their derivatives and salts. Still more preferably, this cellulosic excipient is selected from the group consisting of hydroxy(C_{2-4} alkyl)-(C_{1-4} alkyl)-celluloses and their derivatives and salts.

Compositions of this embodiment preferably further comprise one or more excipients selected from the group consisting of diluents, disintegrants, binding agents, wetting agents, lubricants and anti-adherent agents. More preferably, these compositions comprise one or more excipients selected from the group consisting of lactose, microcrystalline cellulose, croscarmellose sodium, HPMC, sodium lauryl sulfate, magnesium stearate and talc. Still more preferably, these compositions comprise lactose monohydrate, microcrystalline cellulose, croscarmellose sodium and HPMC, most preferably further comprising one or more additional excipients selected from the group consisting of sodium lauryl sulfate, magnesium stearate and talc.

Individual excipients listed above in the present embodiment optionally can be replaced with other suitable excipients if desired. Acceptable substitute excipients are chemically compatible both with eplerenone and with the other excipients. Although other diluents, disintegrants, binding agents and adhesives, wetting agents, lubricants and/or anti-adherent or glidant agents can be employed, compositions comprising nanoparticulate eplerenone, lactose, microcrystalline cellulose, croscarmellose sodium and HPMC, and, optionally, sodium lauryl sulfate, magnesium stearate and/or talc generally possess a superior combination of pharmacokinetic, chemical and/or physical properties relative to such other compositions.

In another embodiment, a composition of the invention comprises:

about 1% to about 95% eplerenone;

about 5% to about 99% of a pharmaceutically acceptable diluent;

about 0.5% to about 30% of a pharmaceutically acceptable disintegrant; and

about 0.5% to about 25% of a pharmaceutically acceptable binding agent;

all percentages being by weight. Such a composition optionally can additionally

incorporated herein by reference.

EXAMPLES

The following Examples contain detailed descriptions of methods of preparation of various solid state forms of eplerenone described herein. These detailed descriptions fall within the scope of the invention and illustrate the invention without in any way restricting that scope. All percentages are by weight unless otherwise indicated. The eplerenone starting material used in each of the following Examples was prepared in accordance with scheme 1 set forth in above-cited International Patent Publication No. WO 98/25948.

Example 1: Preparation of methyl ethyl ketone solvate from high purity eplerenone starting material and preparation of Form L eplerenone from the solvate

A. Preparation of methyl ethyl ketone solvate

High purity eplerenone (>99% purity with <0.2% total diepoxide and 11,12-epoxide) in an amount of 437 mg was dissolved in 10 ml methyl ethyl ketone by heating to boiling on a hot plate with magnetic stirring at 900 rpm. The resulting solution was allowed to cool to room temperature with continuous magnetic stirring. Once at room temperature, the solution was transferred to a 1°C bath with continued stirring for 1 hour. Solid methyl ethyl ketone solvate was collected from the cold solution by vacuum filtration.

B. Preparation of Form L eplerenone

The solid methyl ethyl ketone solvate prepared as above was dried in an oven at 100°C for four hours at ambient atmospheric pressure. The dried solid was determined to be pure Form L by DSC and XRPD analysis.

Example 2: Preparation of additional solvates from high purity eplerenone starting material

Additional solvated crystalline forms were prepared substantially as in Example 1 by replacing methyl ethyl ketone with each of the following solvents: n-propanol, 2-pentanone, acetic acid, acetone, butyl acetate, chloroform, ethanol, isobutanol, isobutyl acetate, isopropanol, methyl acetate, ethyl propionate, n-butanol, n-octanol, propyl acetate, propylene glycol, t-butanol, tetrahydrofuran and toluene.

impurity as herein defined were prepared by adding the desired amount of the impurity to a 7 ml scintillation vial together with an amount of eplerenone sufficient to provide a total sample mass of 100 mg. The content of the impurity in each sample is given in Tables 6A and 6B, where the impurity is respectively the diepoxide or the 11,12-epoxide. A micro-flea magnetic stirrer was added to each scintillation vial along with 1 ml of methyl ethyl ketone. The vials were loosely capped and the solids were dissolved by heating to reflux on a hot plate with magnetic stirring. When dissolution was complete, the resulting solutions were allowed to cool to room temperature, with continued stirring. The resulting solids were then collected by vacuum filtration and immediately analyzed by XRPD. The solids were then placed in a 100°C oven and dried for 1 hour at ambient atmospheric pressure. The dried solids were analyzed by XRPD for Form H content by monitoring the area of the Form H diffraction peak at about 12.1 degrees 2θ. All XRPD diffraction patterns were recorded using an Inel Multipurpose diffractometer.

Table 6A: Composition of eplerenone starting materials in Example 6

% Diepoxide	Eplerenone (mg)	Diepoxide (mg)
0	100.44	0
1	99.08	1.24
2	98.09	2.24
3	97.08	3.04
5	95.09	5.04

Table 6B: Composition of eplerenone starting materials in Example 6

% 11,12-Epoxide	Eplerenone (mg)	11,12-Epoxide (mg)
0	101.38	0
1	99.23	1.10
5	94.97	5.36
10	90.13	10.86

A. Diepoxide results

Fig. 13 shows the XRPD patterns for methyl ethyl ketone solvate wet cake obtained from the (a) 0%, (b) 1%, (c) 3% and (d) 5% diepoxide-doped methyl ethyl ketone crystallizations. The peak intensities have been normalized for ease of comparison. No peaks characteristic of Form H or of the diepoxide are present in the diffraction patterns. The patterns are characteristic of the methyl ethyl ketone solvate of eplerenone.

The Form H seeding experiment (where high purity eplerenone was seeded with Form H) yielded a product that was 77% Form H based on XRPD analysis, but entirely Form H based on DSC. The XRPD model, however, had not been tested for linearity beyond about 15% Form H. This experiment was the only one of the four experiments of this Example where Form H was created in the absence of the diepoxide.

The Form L seeding experiment (where low purity eplerenone was seeded with Form L) yielded a product that was entirely Form L.

The data obtained for high condition fluid bed drying of eplerenone appeared to correspond to the data obtained for vacuum oven drying. The low condition fluid bed drying yielded results that differed from those for vacuum oven drying.

Table 7A: Results of Example 7

Cooling rate (°C/min.)	Cooling endpoint (°C)	Starting material % purity	Nucleation temp. (°C)	% 11,12-Epoxide[1]	% Diepoxide[1]	Assay for desolvated crystal	% yield	% Form H (by XRPD)
3	45	94.5	57.0	ND	ND	100.3	66.1	ND
3	5	94.5	54.9	ND	ND	100.3	98.1	ND
0.1	45	94.5	60.9	ND	ND	100.3		ND
0.1	5	94.5	63.4	ND	ND	100.5	79.3	ND
3	45	61.1		4.8	36.6	43.3	27	100[2]
3	45	89.3	52.2	0.49	0.88	98.3	62	29
3	5	89.3	53.3	0.56	1.0	98.1	87	9
1.5	25	100	59.0	0.18	0.36	99.4	75	5
0.1	45	89.3	63.3	0.20	0.44	99.4	36	31
0.1	5	89.3	61.4	0.18	0.40	99.5	87	ND
1.5	25	100	60.6	0.18	0.36	99.5	79.2	ND
1.5	25	100	55.9	0.38	0.80	98.6	80.5	<3%
1.5	25	100 seeded Form H		0.03	ND	100.4	82.2	77/100[3]
1.5	25	89.3 seeded Form L		0.33	0.50	97.5	80.2	ND

[1] Weight % after drying solvate in a vacuum oven at 75°C.

[2] Appears to be mixture of Form H and diepoxide when analyzed by XPRD.

[3] Appears to be 77% Form H by XPRD and 100% Form H by DSC.

ND = none detected.

F. Material purity

A cube plot of product purity, starting material purity, cooling rate and endpoint temperature based on the data reported in Table 7A is shown in Fig. 18. The cube plot suggests that use of a higher purity material at the start of crystallization will

yield a higher purity product. The endpoint temperature of crystallization does not appear greatly to affect product purity. The cooling rate, however, appears to have an effect with slightly less pure product resulting from a faster cooling rate. In fact, the level of diepoxide generally was higher with faster cooling rates.

Fig. 19 shows a half normal plot that was prepared using the results of the cube plot to determine which variables, if any, had a statistically significant effect on product purity. Starting material purity had the greatest statistically significant effect on product purity, although the effect of cooling rate and the interaction between cooling rate and starting material purity were also seen as statistically significant.

Fig. 20 is an interaction graph based on these results, showing the interaction between starting material purity and cooling rate on product purity. With the high purity eplerenone the cooling rate appears to have little or no effect on final purity. With the low purity eplerenone (89.3% eplerenone starting material), however, the product purity decreases as cooling rate increases. This result suggests that more impurities crystallize out when crystallization is conducted at higher cooling rates.

G. Form H content

A cube plot of Form H weight fraction, starting material product purity, cooling rate and endpoint temperature based on the data reported in Table 7A is shown in Fig. 21. The cube plot suggests that use of a higher purity eplerenone at the start of crystallization will yield a lower amount of Form H. The endpoint temperature of crystallization also appears to have an effect on the form of the final product. The cooling rate does not appear to greatly affect the formation of Form H although some Form H may result from faster cooling at the low endpoint temperature in the presence of impurities.

Fig. 22 shows a half normal plot that was prepared using the results of the cube plot to determine which variables, if any, had a statistically significant effect on the amount of Form H in the final material. Starting material purity, endpoint temperature of the crystallization and the interaction between these two variables were seen as statistically significant effects.

Fig. 23 is an interaction graph based on these results, showing the interaction between starting material purity and endpoint temperature on final Form H content. With the high purity eplerenone, endpoint temperature appears to have little effect on

combined with 126 ml of ethanol 3A. The slurry was heated to reflux and the distillate removed. An additional 126 ml of ethanol 3A was simultaneously added as 126 ml of solvent was removed via atmospheric distillation. Upon completion of the solvent turnover, the mixture was cooled to 25°C and stirred for 1 hour. The resulting solid was filtered and rinsed with ethanol 3A, and was then air-dried to yield the ethanol solvate. The solvate was further dried in a vacuum oven at 90-100°C for 6 hours to obtain 14.9 g of Form H eplerenone.

B. Digestion with methyl ethyl ketone solvent

In an alternative digestion process, 1 g of low purity eplerenone (about 65% assay) was digested in 4 ml methyl ethyl ketone for 2 hours, after which the mixture was allowed to cool to room temperature. Once cooled, the resulting solid was collected by vacuum filtration and determined to be the methyl ethyl ketone solvate by XRPD analysis. The solid was dried at 100°C for 30 to 60 minutes. The dried solid was determined to be pure Form H by XPRD.

Example 10: Digestion of high purity eplerenone with a solvent to prepare Form L

A. Digestion with ethanol solvent

High purity eplerenone in an amount of 1 g was digested in 8 ml ethanol for approximately 2 hours. The solution was then allowed to cool to room temperature and the solids were collected by vacuum filtration. Analysis of the solids by XRPD immediately after filtration indicated that the solids were a solvate (presumably the ethanol solvate). The solids were subsequently dried at 100°C at ambient atmospheric pressure for 30 minutes. The dried solids were analyzed by XRPD and determined to be predominantly Form L (no Form H was detected).

B. Digestion with methyl ethyl ketone solvent

High purity eplerenone in an amount of 1 g was digested in 4 ml methyl ethyl ketone for 2 hours, after which the solution was allowed to cool to room temperature and the solids were collected by vacuum filtration. The solids were immediately analyzed by XRPD and determined to be a solvate of eplerenone (presumably the methyl ethyl ketone solvate). The solvate was subsequently dried at 100°C at ambient atmospheric pressure for 30 to 60 minutes. The dried solids were analyzed by XRPD and determined to be primarily Form L with no diffraction peaks for Form H present.

Procedure E

In another alternative procedure, 5.0 g eplerenone (purity >99%) was added to 82 g (104 ml) methanol. Under stirring action at 210 rpm, the solution was heated to 60°C and held at that temperature for 20 minutes to ensure complete dissolution. The solution was then cooled to –5°C at a rate of 0.16°C/minute under stirring. The resulting crystals were collected by filtration and dried in a vacuum oven at 40°C for 20 hours. The dried solids were determined to be pure Form L eplerenone by DSC and XRPD analysis.

Procedure F

In an alternative procedure, 6.0 g eplerenone (ethanol solvate containing 9% ethanol and having a corrected purity of 95.2%) was added to 82 g (104 ml) methanol. Under stirring action at 210 rpm, the solution was heated to 60°C and held at that temperature for 20 minutes to ensure complete dissolution. The solution was then cooled to 50°C at a rate of 0.14°C/minute and then held at that temperature for about 2.5 hours. The solution was then cooled to –5°C at a rate of 0.13°C/minute under stirring. Crystals were collected by filtration and dried in a vacuum oven at 40°C for 16 hours. The dried solids were determined to be pure Form L eplerenone by DSC and XRPD analysis.

Example 12: Crystallization of Form H directly from solution

The diepoxide in an amount of 150.5 mg and eplerenone in an amount of 2.85 g were added to 1.5 ml nitrobenzene. The mixture was magnetically stirred at 200°C for several hours. The resulting slurry was then allowed to cool to room temperature by natural air convection. The sample was dried and analyzed by polarized light microscopy and XRPD. The XPRD analysis indicated that the sample was a mixture of Form H and Form L. The crystals were translucent by microscopy, indicating that desolvation (and conversion to either Form H or Form L) did not occur.

Example 13: Preparation of amorphous eplerenone by comminution

Approximately one-half of a steel Wig-L-Bug container was filled with about 60 g eplerenone (>99.9% purity). A steel ball and cap were placed on the sample container and agitated for 30 seconds by the Wig-L-Bug apparatus. The eplerenone

was scraped off the surface of the Wig-L-Bug container and the container agitated for an additional 30 seconds. The resulting solid was analyzed by XRPD and DSC and was determined to be a mixture of amorphous eplerenone and Form L crystalline eplerenone.

Example 14: Preparation of amorphous eplerenone by lyophilization

Approximately 100 mg of crude eplerenone was weighed into a beaker containing 400 ml water. The resulting mixture was heated slightly for 5 minutes, and then sonicated and heated with stirring for an additional 5 minutes to provide a dispersion. Approximately 350 ml of the eplerenone dispersion was filtered into a 1000 ml round bottom flask containing 50 ml of HPLC water. The dispersion was flash frozen in a dry ice/acetone bath over a time period of 1-2 minutes. The flask was attached to a Labconco Freezone 4.5 freeze dryer and the contents dried overnight. The solids in the flask were transferred to a small brown bottle. A small aliquot was observed under polarized light microscopy at 10X, 1.25X optivar in cargille oil (1.404) and observed to be at least 95% amorphous eplerenone. Figures 24 and 25 show the XRPD pattern and DSC thermogram obtained for the amorphous eplerenone. The peak observed at 39 degrees 2θ in Fig. 24 is attributable to the aluminum sample container.

Example 15: Solubility of Form L eplerenone

The aqueous solubility of Form L eplerenone was measured at pH 7 (100 mM phosphate buffer) at 5, 25 and 40°C. Approximately 30 mg of Form L eplerenone was mixed with approximately 10 ml of buffer to form a slurry of eplerenone at both 5 and 25°C. Approximately 40 mg of Form II eplerenone was mixed with approximately 10 ml of buffer to form a slurry of eplerenone at 40°C. Samples were prepared in duplicate for each condition. The slurries were allowed to equilibrate in water shaker baths at the appropriate temperature and the solutions were analyzed for eplerenone content by ultraviolet visible analysis (245 nm) at time intervals of 1, 5, 12, 19, 27 and 36 days. Data from each temperature were appropriately averaged to determine the solubility of eplerenone at each temperature and are reported in Table 8. The residual solids from each time point were analyzed by DSC and TGA at the end of the 36 day equilibration and were determined to be Form L eplerenone.

Table 8: Solubility of Form L eplerenone

Temperature (°C)	Form L solubility (mg/ml)
5	0.24
25	0.29
40	0.39

Example 16: Measurement of Intrinsic Dissolution Rates

Intrinsic dissolution rates were measured for the following four eplerenone polymorph samples: (i) Form L eplerenone prepared by direct crystallization from acetonitrile using water as an anti-solvent in the same manner as in Example 11, Procedure B; (ii) Form H eplerenone prepared by digestion in ethanol in the same manner as in Example 10, Procedure A, (iii) a mixture of 5% Form H and 95% Form L; and (iv) Form L eplerenone that was micronized to provide the following particle size distribution: 10% by weight of the particles under 9 μm, 50% by weight of the particles under 22 μm, and 90% by weight of the particles under 41 μm.

Eplerenone in an amount of 150 mg was weighed and placed into a VanKel intrinsic dissolution cavity. The powder was compressed at 8280 kPa using a Carver press to form tablets. The sample was then mounted on the intrinsic dissolution apparatus. The dissolution medium used was 1% sodium dodecyl sulfate (SDS) in HPLC water. All tests were conducted at 37°C for 2 hours. Before the start of the experiment, 500 ml of the dissolution medium was equilibrated at 37°C for 30 minutes in the dissolution bathing chamber. An initial sample was taken from each dissolution vessel, serving as the initiation time (T_0) for the test. The eplerenone tablets were then lowered into the dissolution medium. Samples were drawn at determined intervals for the determination of rate of dissolution. Care was taken to avoid air bubbles forming at the surface of the tablet. The samples were analyzed by UV absorbance detection at 243 nm. Intrinsic dissolution rates were calculated from the slope of the linear portion of the concentration versus time profiles corrected for volume and normalized for the surface area of the dissolution tablet (0.5 cm^2).

Fig. 26 reports the intrinsic dissolution rates measured for the four samples. These studies indicate that Form H eplerenone has faster intrinsic dissolution rate than Form L eplerenone. XRPD measurements comparing compressed and uncompressed eplerenone confirmed that the polymorphs did not interconvert upon compression or

The dogs were fasted for 15 to 20 hours prior to administration of the capsule and were not fed again until at least 4 hours after dose administration. Blood samples (approximately 3 ml) were collected by venipuncture in chilled tubes containing heparin at 0, 0.5, 1, 2, 3, 4, 6, 8 and 24 hours after dose administration. The blood samples were immediately placed on ice. Separation of plasma from the blood samples was complete after about 15 minutes of centrifugation. The resulting plasma samples were frozen at about –20°C and stored until analyzed. Analysis was performed using an LC/MS/MS procedure.

The same four dogs were used for testing three formulations, each having the composition shown in Table 12 but having different eplerenone particle sizes. The eplerenone starting materials had D_{90} particle sizes of about 212 μm, about 86 μm and about 36 μm, respectively. A minimum wash-out period of 5 days was allowed between administration of successive formulations. The mean results are reported in Tables 13 and 14 below. Relative bioavailability was calculated from the AUC result, the formulation having D_{90} of 86 μm being selected as the standard.

Table 13: Blood serum eplerenone concentration (μg/ml), Example 21

Time (hours)	D_{90} 212 μm	D_{90} 86 μm	D_{90} 36 μm
0	0	0	0
0.5	1.83	3.65	1.99
1	2.40	6.18	5.86
2	3.77	6.89	6.77
3	2.85	5.70	6.60
4	2.61	4.39	5.56
6	1.63	3.11	3.31
8	1.10	1.90	2.09
24	0.0252	0.032	0.0706

Table 14: Pharmacokinetic (PK) parameters calculated from data of Example 21

PK parameter	D_{90} 212 μm	D_{90} 86 μm	D_{90} 36 μm
C_{max} (μg/ml)	3.98	7.02	7.39
T_{max} (hours)	1.50	1.75	2.25
AUC ((μg/ml)hr)	26.6	49.2	53.1
Relative bioavailability (%)	53.25	100	107.9